REMARKS

I. Pending Claims

Claims 1-20 are currently pending in the instant application. Claims 14-16 are under active consideration. Claims 14 and 16 have been amended. Applicants expressly do not disclaim the subject matter of any invention disclosed herein which is not set forth in the instantly filed claims. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications.

II. Support for the Amendments

Part b) of claims 14 and 16 have been amended to recite, "said polynucleotide encodes a polypeptide having methyltransferase activity". Support for this amendment may be found in the Specification, at least, at page 3, lines 2-4, wherein it is set forth that SEQ ID NO:1 is a human S-adenosyl-L-methionine methyltransferase called SAM-MT. No new matter is added by this amendment.

In addition, in claim 14, the phrase, "and which probe specifically hybridizes to said target polynucleotides" has been removed. Further, as the Examiner has suggested, Applicants have amended claims 14 and 16 to recite that the a polynucleotide sequence is completely complementary to the polynucleotide of a) or b).

III. Indefiniteness rejection under 35 U.S.C. § 112, second paragraph

The Examiner has maintained the rejection of claims 14 and 15 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner has stated that claim 14 (and 15, dependent therefrom) is indefinite since the phrase "specifically hybridizes" is allegedly not defined in the specification (Office Action mailed November 4, 2003; page 3). While not acquiescing to the position of the Patent Office, part b) of claims 14 and 16 have been amended to recite, "said polynucleotide encodes a polypeptide having methyltransferase activity". In addition, in claim 14, the phrase, "and which probe specifically hybridizes to said target polynucleotides" has been removed. Further, claim

16 has been amended to recite, "a polynucleotide completely complementary to the polynucleotide of a)". These amendments serve to further clarify the subject matter which Applicants consider to be the invention. Applicants are amending the claim solely to obtain expeditious allowance of the instant application. Support for these amendments may be found in the Specification, at least, at page 3, lines 2-4, wherein it is set forth that SEQ ID NO:1 is a human S-adenosyl-L-methionine methyltransferase called SAM-MT. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include polypeptides or fragments having biological activities in addition to enzymatic activity. Applicants submit that this amendment obviates this rejection. Therefore, reconsideration and withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

IV. Written description rejection under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 14-16 under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. This rejection is respectfully traversed for the reasons made of record in the response filed on August 21, 2003.

Please note that part b) of claims 14 and 16 have been amended to recite, "said polynucleotide encodes a polypeptide having methyltransferase activity". In addition, in claim 14, the phrase, "and which probe specifically hybridizes to said target polynucleotides" has been removed. These amendments serve to further describe the subject matter which Applicants consider to be the invention.

A. No description of the function of the polynucleotides is required to satisfy the written description requirement for the claimed methods of detecting the target polynucleotides

The written description requirement does not require Applicants to disclose the function of the polynucleotides referenced in the claimed methods of detecting the claimed polynucleotides and fragments thereof. In the Office Action, the Examiner attempts to introduce a "functional limitation" to the target polynucleotides of the claims, limitations which are not present in claims 14-16.

Applicants respectfully remind the Examiner that disclosure of functional characteristics is merely one of the factors which can be used as evidence that Applicants were in possession of the claimed invention at the time of filing. In addition, functional limitations are not necessary as the structural and source limitations are sufficient to describe the target polynucleotides of the claims and in any case, "biological function" is irrelevant to the use of the claimed methods and target polynucleotides of the claims in toxicology testing (Infra. Section V).

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are also well-established by case law:

> ...the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed* (Vas-Cath, Inc. v. Mahurkar, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (emphasis added)).

The Examiner's position is clearly contrary to the USPTO's own written description guidelines ("Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, para. 1", published January 5, 2001), which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met (footnotes omitted; emphasis added).

B. The specification provides an adequate written description of the structure of the target polynucleotides of the claims

The subject matter encompassed by claims 14-16 is either disclosed by the Specification or is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the Specification (see, for

example, the Sequence Listing at pages 54-56). Variants of SEQ ID NO:1 and SEQ ID NO:2 are described, e.g., at page 3, lines 14-15, page 13, lines 13-21, page 14, lines 25-29, page 15, lines 5-12, and page 37, lines 1-10. Incyte clones in which the nucleic acids encoding the human SAM-MT were first identified and libraries from which those clones were isolated are described, for example, at page 13, line 28 through page 14, line 4 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, at page 14, lines 5-19. The Specification describes (e.g., page 45, lines 1-21) how to use BLAST to determine whether a given sequence falls within the "at least 90% identical" scope. Complementary sequences are described, e.g., at page 8, lines 6-9, page 8, lines 20-28, page 11, lines 10-12, and page 49, lines 12-21. RNA equivalents are described, e.g., at page 11, lines 10-12 and page 36, lines 26-27.

One of ordinary skill in the art would recognize the target polynucleotides of the claims. Given SEQ ID NO:2, one of ordinary skill in the art would recognize a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2. Accordingly, the specification provides an adequate written description of the structure of the claimed genus of polynucleotides, upon which the claimed methods are based.

There is simply no requirement that the claims recite, for example, particular variant polynucleotide sequences because the claims already provide sufficient structural definition of the claimed subject matter. That is, the polynucleotide variants are defined in terms of SEQ ID NO:2 ("...a polynucleotide comprising...a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2"). Because the claimed polynucleotide variants, as well as the claimed complementary sequences and RNA equivalents, are defined in terms of SEQ ID NO:2, the precise chemical structure of every target polynucleotide within the scope of the claims can be discerned. The Examiner's position is nothing more than a misguided attempt to require Applicants to unduly limit the scope of their claimed invention.

The Examiner also states that claims 14-16 "are directed to **all** possible methods for detecting **any** target polynucleotide of claim 12" (Office Action mailed May 16, 2003; page 5; emphasis added). To the contrary. The Examiner has misinterpreted Applicants' claims. Applicants' claims are restricted to the detection of polynucleotides from five specific groups: "a) a polynucleotide comprising a

polynucleotide sequence of SEQ ID NO:2, b) a polynucleotide comprising a naturally occurring polynucleotide at least 90% identical to a polynucleotide sequence of SEQ ID NO:2, c) a polynucleotide complementary to a polynucleotide of a), d) a polynucleotide complementary to a polynucleotide of b), and e) an RNA equivalent of a)-d). Thus, only those sequences that share 90% sequence identity with SEQ ID NO:2 are claimed; certainly many others could be detected. Moreover, Applicants have further limited the claims to the detection of "naturally occurring" variants of SEQ ID NO:2.

The Specification at page 6, lines 3-6, defines "SAM-MT" as "the amino acid sequences of substantially purified SAM-MT obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human, from any source whether natural, synthetic, semi-synthetic, or recombinant." Hence, it is apparent that the inventors contemplated naturally occurring variants of SEQ ID NO:1.

The term "naturally occurring" is a well-known term in the art which Applicants intended to be used in such context. As such, no further definition of the term is necessary (MPEP 2163 IIA3(a)):

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

One of ordinary skill in the art would recognize that "***a naturally occurring polynucleotide sequence***" as recited in claim 14 is one which occurs in nature. Through the process of natural selection, nature will have determined the appropriate nucleic acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of SAM-MT) and SEQ ID NO:2 (the polynucleotide sequence encoding SAM-MT), one of skill in the art would be able to routinely obtain "a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the

subject application was filed and/or described throughout the Specification of the instant application.

C. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to methods of detecting specific polynucleotides) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define methods of detecting polynucleotides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claim 14, as amended, recites chemical structure to define the claimed genus:

> 14. (Currently Amended) A method for detecting a target polynucleotide in a sample, said target polynucleotide, selected from the group consisting of:
> a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2,
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2, said polynucleotide encodes a polypeptide having methyltransferase activity,
> c) a polynucleotide completely complementary to a polynucleotide of a),
> d) a polynucleotide completely complementary to a polynucleotide of b), and
> e) an RNA equivalent of a)-d); the method comprising:
> i) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and
> ii) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides recited by the claims. The polynucleotides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

D. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope. In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078; Attachment No. 3). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that >40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to polynucleotides encoding polypeptides related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as SAM-MT proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides comprising "a naturally occurring polynucleotide sequence at least

90% identical to the polynucleotide sequence of SEQ ID NO:2." This variation is far less than that of all potential SAM-MT proteins related to SEQ ID NO:1; i.e., those SAM-MT proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

E. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 25, 1997. Much has happened in the development of recombinant DNA technology in the 17 years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the target polynucleotides of the claims at the time of filing of this application.

F. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus

of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above. Applicants have provided an adequate written description of the claimed methods of detecting the target polynucleotides and fragments thereof.

Accordingly, Applicants request that the Examiner withdraw the written description rejection under 35 U.S.C. § 112, first paragraph.

V. Enablement rejection under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 14-16 under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed methods of detecting the recited polynucleotides and fragments thereof. Applicants respectfully disagree and traverse the rejection for the reasons made of record in the response filed on August 21, 2003.

In addition, since the current amendments limit the claimed invention to methods of detecting the polynucleotide sequence of SEQ ID NO:2, Applicants believe that the Examiner should find the Specification enabling in light of the current amendments.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than **objective enablement**. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Applicants submit that the disclosure amply enables the claimed invention. Given the sequence

of SEQ ID NO: 2, one of ordinary skill in the art could readily identify a polynucleotide encoding a polypeptide comprising a naturally occurring polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO: 2, using well known methods of sequence analysis without any undue experimentation. For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the Specification of the instant application. See, e.g., page 16, line 5 through page 17, line 19; page 37, lines 1-21; and Example VI at page 48. Thus, one skilled in the art need not make and test vast numbers of polynucleotides. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides that already exist in nature. The skilled artisan would also know how to use the claimed polynucleotides, for example in expression profiling, disease diagnosis, or detection of related sequences as discussed above. The specification also describes the expression vectors into which the claimed variants and fragments could be inserted, and the construction of fusion proteins (pages 20-31 and Example IX at page 50).

Applicants respectfully point out that the claims of the instant application are drawn to **naturally occurring** variants. Thus it is not necessary to screen every conceivable variant which might be made using recombinant methods, as all that is claimed are those variant sequences which are found in nature. Through the process of natural selection, nature will have determined the appropriate sequences.

Furthermore, the claims are directed to polynucleotides, not polypeptides, and it is the functionality of the claimed polynucleotides, not the polypeptides encoded by them, that is relevant. Members of the claimed genus of variants may include, for example, mutant alleles associated with diseases, or single nucleotide polymorphisms (SNPs). Members of the claimed genus of variants may be useful even if they encode defective SAM-MT polypeptides. For example, the variant polynucleotides could be used for the detection of sequences related to SAM-MT (see the specification, for example, at pages 38-39) including SAM-MT variants that may be associated with disease states, such as the diseases listed on pages 37-38 of the specification. See the specification at, for example, pages 39-43 for disclosure of how to use the claimed sequences in diagnostic assays.

Further, the Examiner requires working examples. There is no such requirement under the law to provide "working examples." As set forth in *In re Borkowski,* 164 USPQ 642, 645 (CCPA 1970) (footnote omitted):

> However, as we have stated in a number of opinions, a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation.

See also M.P.E.P. 2164.02 as follows:

> Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic"... A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

Thus, there is no requirement under the law to provide "working examples" of what is claimed. Rather, one looks to whether the specification provides a description of how to make what is claimed. The present specification provides the requisite description.

Contrary to the standard set forth in *Marzocchi* and *Borkowski*, the Examiner has failed to provide any ***reasons*** why one would doubt that the guidance provided by the present specification would enable one to make and use the recited polynucleotides. Hence, a *prima facie* case for non-enablement has not been established. For at least the above reasons, withdrawal of the enablement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

A. How to make

The Specification provides sufficient teaching of the manner and process of *making* the invention. SEQ ID NO:1 and SEQ ID NO:2 are specifically disclosed in the Specification (see, for example, the Sequence Listing at pages 54-56). Variants of SEQ ID NO:1 and SEQ ID NO:2 are described, e.g., at page 3, lines 14-15, page 13, lines 13-21, page 14, lines 25-29, page 15, lines 5-12, and page 37, lines 1-10. Incyte clones in which the nucleic acids encoding the human SAM-MT were first identified and libraries from which those clones were isolated are described, for example, at page 13, line 28 through page 14, line 4 of the Specification. Chemical and structural features of SEQ ID NO:1 are described, for example, at page 14, lines 5-19. "Naturally occurring" polynucleotide

sequences occur in nature; they are not created exclusively in a laboratory. The Specification describes how to find naturally occurring homologs in other individuals and species (e.g., page 37, lines 1-3) and how to use CLUSTAL V and BLAST to determine whether a given naturally occurring polynucleotide sequence falls within the "at least 90% identical to a polynucleotide sequence of SEQ ID NO:2" scope (e.g., page 45, lines 1-21).

The making of the target polynucleotides of the claims by recombinant and chemical synthetic methods is disclosed in the Specification, at, e.g., page 18, lines 27-30, page 19, line 13 through page 24, line 14, and page 31, lines 22-29. The making of the probes of the claims is disclosed in the Specification, e.g, at page 24, line 24 through page 25, line 7, page 37, lines 1-21, page 39, lines 20-27, page 40, line 16 through page 42, line 3, page 48, lines 23-33, and page 49, lines 9-30. This satisfies the "how to make" requirement of 35 U.S.C. § 112, first paragraph.

B. How to use

Applicants' invention is directed, *inter alia*, to methods of detecting polynucleotides encoding polypeptides having homology to Caenorhabditis elegans putative methyltransferase (GI 1065505). The claimed methods and target polynucleotides have a variety of utilities, in particular in expression profiling, and in particular for diagnosis of conditions or diseases characterized by expression of SEQ ID NO:1 (SAM-MT), for toxicology testing, and for drug discovery (see the Bandman '933 Specification at, e.g., page 36, line 25 through page 42, line 3). As described in the Specification:

> Nucleic acids encoding the SAM-MT of the present invention were first identified in Incyte Clone 10625 from the THP-1 promonocyte cell line, PMA+LPS stimulated, cDNA library (THP1PLB01) using a computer search for amino acid sequence alignments. A consensus sequence, SEQ ID NO:2, was derived from the following overlapping and/or extended nucleic acid sequences: Incyte Clones 10625 (THP1PLB01), 1749286 (STOMTUT02), 1689223 (PROSTUT10), 075978 (THP1PEB01), and 2731022 (OVARTUT04).
>
> In one embodiment, the invention encompasses a polypeptide comprising the amino acid sequence of SEQ ID NO:1, as shown in Figs. 1A, 1B, and 1C. SAM-MT is 281 amino acids in length, with a predicted relative molecular mass of 31.9 kDa (MacDNASIS PRO software). SAM-MT has three potential protein kinase C phosphorylation sites at residues S-194, S-240, and T-273, and one potential tyrosine kinase phosphorylation site at residue Y-48. As shown in Figs. 2A and 2B, SAM-MT has chemical and structural homology with the putative methyltransferases from C.

elegans (GI 1065505; SEQ ID NO:3) and S. cerevisiae (GI 1907189; SEQ ID NO:4). In particular, SAM-MT and C. elegans putative methyltransferase share 51% amino acid sequence identity, share the AdoMet-MT motifs I and III, and share one protein kinase C phosphorylation site. As illustrated by Figs. 3A and 3B, SAM-MT and C. elegans putative methyltransferase have rather similar hydrophobicity plots. As shown in Figs. 4A and 4B, SAM-MT contains three common consensus sequence motifs of the small molecule methyltransferase enzymes (AdoMet-MT) that utilize AdoMet as a substrate or product.

Northern analysis shows the expression of this sequence shows expression in various libraries, at least 60% of which are immortalized or cancerous, 50% are from secretory tissue, and at least 41% of which involve immune response. Of particular note is the expression of SAM-MT in gut, reproductive, and neural tissue; in proliferating cells; in fetal lung, gut, and heart; and in placenta.
(See the '933 Bandman Specification at page 13, line 28 through page 14, line 19).

VI. Claim Rejections – 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 14-16 under 35 U.S.C. 103(a) as being unpatentable over Boker et al. (Journal of Biological Chemistry, Vol. 269, No. 26, pages 17697-17704, 1994, and Hillier et al. (Wash-Merck EST Project, GENBANK Accession Number AA054310, December 1996). The Examiner alleges that one of ordinary skill in the art would have been motivated to use the nucleotide sequence disclosed by Hillier et al. to detect and isolate a full length methyltransferase cDNA clone, in view of the teachings of Boker et al., thus rendering the instant invention obvious. Applicants respectfully disagree and traverse the rejection for the reasons made of record in the response filed on August 21, 2003.

Further, the current amendments limit the claimed invention to methods of detecting the polynucleotide sequence of SEQ ID NO:2, and this sequence is not disclosed by the cited reference. The Hillier reference does not teach or suggest the entirety of Applicants claimed invention. Therefore, would be no motivation to combine the cited references, and claims 14-16 cannot be rendered obvious.

Applicants' rejected claims, as amended, are as follows:

14. (Currently Amended) A method for detecting a target polynucleotide in a sample, said target polynucleotide, selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising a naturally occurring polynucleotide

sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2, said polynucleotide encodes a polypeptide having methyltransferase activity,

c) a polynucleotide completely complementary to a polynucleotide of a),

d) a polynucleotide completely complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d); the method comprising:

i) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

ii) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

15. (Original) A method of claim 14, wherein the probe comprises at least 60 contiguous nucleotides.

16. (Currently Amended) A method for detecting a target polynucleotide in a sample, said target polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence of SEQ ID NO:2,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence of SEQ ID NO:2,said polynucleotide encodes a polypeptide having methyltransferase activity,

c) a polynucleotide completely complementary to a polynucleotide of a),

d) a polynucleotide completely complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d); the method comprising:

i) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

ii) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

Hillier et al. disclose a 463 nucleotide human cDNA fragment. SEQ ID NO:2 is 672 nucleotides longer than the Hillier fragment. The Hillier et al. reference does not disclose that the cited AA054310 fragment encodes a methyltransferase. In addition, the Bokar et al. reference does not disclose any sequence.

Applicants note that in all three of the claims, drawn to methods of detecting specific polynucleotides, the preamble to the claim contains the implicit limitation "said target polynucleotide having a sequence of a polynucleotide of claim 12," as in claims 14-16 (which were amended to incorporate all of the limitations of claim 12). In this case, the preamble "breathes life and meaning" into the claim and thus is a limitation which is **not** taught by the prior art. Moreover, it should be noted that the product of these methods is a complex or other product necessarily defined by the novel sequences of claims 14-16, as currently amended.

A. The Examiner has mischaracterized the claims

First and foremost, this rejection is inappropriate because the Examiner has failed to cite any references which, either alone or in combination, would render obvious the claimed methods, which relate to methods of detecting a specific, particular sequence.

Applicants do not claim a method for detecting all polynucleotides encoding methyltransferases. Applicants claim a method for detecting **the** polynucleotides of claim 12, which are referred to in claims 14-16, as currently amended. The Examiner continues to improperly construe the claim language by failing to give weight to the limitation of the preamble, "said target polynucleotide having a sequence of a polynucleotide of claim 12."

As was discussed in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 51 USPQ2d 1161 (Fed. Cir 1999):

> If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is "necessary to give life, meaning, and vitality" to the claim, then the claim preamble should be construed as if in the balance of the claim. *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 480-81 (CCPA 1951); see also, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997); *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989). Indeed, when discussing the "claim" in such a circumstance, there is no meaningful distinction to be drawn between the claim preamble and the rest of the claim, for only together do they comprise the "claim".

Thus, it is clear that the Examiner cannot disregard the limitation recited in the preamble, i.e., that the product detected is a specific sequence, and that sequence is not only novel, it is unobvious

itself . Yet, this is what the Examiner has done. Applicants have already received a patent on SEQ ID NO:2. Therefore, it is free from prior art.

To constitute an obviousness rejection under 35 U.S.C. 103(a), the cited reference must teach each and every limitation of the claimed invention. Hillier et al. does not teach SEQ ID NO:2. Accordingly, the combined cited prior art does not teach or suggest each and every limitation of claims 14-16. When claims 14-16 are properly construed, they are not obvious under 35 U.S.C. 103(a).

B. Failure to establish a prima facie case of obviousness

The Examiner has asserted that, one of ordinary skill in the art would have been motivated to use the polynucleotide of Hillier et al., "to detect an isolate a full length human methyltransferase cDNA clone, to lead to a better understanding of the underlying complexity of the methylation of nucleic acids as a post-transcriptional modification mechanism" (Office Action of May 16, 2003; page 10). Applicants respectfully traverse this rejection on the ground that the Examiner has clearly failed to establish a proper *prima facie* case of obviousness.

1. Hindsight reconstruction

The nucleic acid sequence of SEQ ID NO:2 and the corresponding the full-length sequence of the human S-adenosyl-L-methionine methyltransferase gene was not known until Applicants elucidated it.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. The rejection focuses on the probes used in the claimed methods, and asserts that the Hillier et al. document makes obvious the identity of particular probes which could be used to practice the recited methods of detection. Following this logic, the Examiner concludes that the methods are obvious because the probes are obvious. It may be possible that such logic would apply if the recited methods were directed to detecting **any** target polynucleotide which hybridizes to probes generated from the sequence of Hillier et al. However, this is not the case with the recited methods of detection. The claims in question recite methods of detecting specific target polynucleotides which are disclosed in the specification. For example, claim 14,

implicitly recites a method of detecting a target polynucleotide in a sample, i.e., a polynucleotide having a sequence of a polynucleotide of former claim 12.

The rejection is not supported because it ignores the limitation that the claims are directed to detecting specific **target polynucleotides**, disclosed in the specification. One cannot practice the recited methods of detecting a target polynucleotide if one does not know the identity of that target polynucleotide, or even whether that target polynucleotide exists. Without knowledge of a target polynucleotide, one would not have any conception of practicing a method of detecting it, one would not have any motivation to attempt to detect it, and one would certainly not have the ability to detect it. By focusing on the alleged obviousness of the probes used in the claimed methods, the Examiner has ignored the fact that the claimed methods require detection of the recited **target polynucleotides**. Since there is no suggestion or teaching in the art to detect the recited target polynucleotides, one would not have been guided to practice the claimed methods.

Applicants note that the dictionary defines "specific" as "restricted to a particular individual, situation, relation, or effect." (Attachment No. 1; Merriam-Webster's Collegiate Dictionary; Merriam-Webster OnLine: http://www.m-w.com). Hence, the phrase "specifically hybridizes" indicates that the probes of claims 14-16, as currently amended, bind only to the polynucleotides of claim 12 and thus would not by definition bind to any oligomer, if any, taught by Hillier et al. It is well known and an inherent requirement of the method that the primers used in PCR amplification must specifically hybridize to the target polynucleotide.

Furthermore, Hillier et al. do not teach a degenerate probe suitable for use to detect the polynucleotides of claims 14-16, as currently amended. Though one of skill in the art may well attempt to design degenerate probes from especially those which would specifically hybridize to the polynucleotides of claims 14-16, as currently amended, they are not suggested from the Hillier et al. document. Only through ***hindsight***, could one detect the novel, full-length, 1135 nucleotide human S-adenosyl-L-methionine methyltransferase from a sample using the Hillier 463 nucleotide cDNA fragment.

2. Obvious "to try"

No matter how obvious it might have been to try to detect the specific full length sequence claimed in claims 14-16, even assuming, *arguendo*, that it might be obvious to try to detect an unknown full-length sequence based on the existence of a gene encoding a human methyltransferase in the prior art, obvious to try does not support a rejection under 35 U.S.C. § 103.

> ". . . [o]bvious to try" has long been held not to constitute obviousness. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. *In re Deuel*, 34 USPQ2d 1210 (CAFC 1995).

The Examiner alleges that the method of detecting a polynucleotide of SEQ ID NO:2 is obvious because a human cDNA fragment encoding a methyltransferase (e.g., the cited Hillier et al. reference) was identified. However, it is respectfully pointed out that the methyltransferase fragment was NOT identified as being a part of Applicants' claimed sequence of SEQ ID NO:2, which had not yet been elucidated. Accordingly, at most the combined cited prior art suggest that is would be obvious to try to clone a full-length sequence of the human S-adenosyl-L-methionine methyltransferase gene. Yet, as stated in *In re O'Farrell* ". . . [o]bvious to try" is not a standard for obviousness under 35 U.S.C. § 103.

Applicants respectfully submit that the rejection fails to state a proper *prima facie* case of obviousness, and that the rejection should, therefore, be withdrawn.

C. Summary

The combined cited prior art does not teach or suggest the detection of the target polynucleotides recited in claims 14-16. Since this reference does not teach or suggest **all** of the claim limitations, the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103 have not been met.

For at least the above reasons, Applicants request that the Examiner withdraw the rejection of claims 14-16 under 35 U.S.C. 103(a) as being unpatentable over Boker et al. and Hillier et al.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE CORPORATION

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